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MEMORANDUM

SUBJECT: Difenoconazole: Preliminary Problem Formulation for Environmental Fate, Ecological Risk, Endangered Species, and Drinking Water Exposure Assessments in Support of Registration Review

FROM: Michael Lowit, Ph.D., Ecologist
Faruque Khan, Ph.D., Senior Fate Scientist
Sujatha Sankula, Ph.D., Branch Chief
Environmental Risk Branch I
Environmental Fate and Effects Division (7507P)

Michael Lowit 2015.11.05 15:24:51 -05'00'

SUJATHA SANKULA

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Date: 2015.11.05 15:46:01 -05'00'

TO: Maria Piansay, Chemical Review Manager
Jill Bloom, Team Leader
Linda Arrington, Branch Chief
Risk Management and Implementation Branch V
Pesticide Re-evaluation Division (7508P)

The Environmental Fate and Effects Division (EFED) has completed the preliminary problem formulation for the environmental fate, ecological risk, endangered species, and drinking water exposure assessments to be conducted as part of the Registration Review of the fungicide difenoconazole (CAS# 119446-68-3). Functioning as the first stage of the risk assessment process for registration review, this problem formulation provides an overview of what is currently known about the environmental fate and ecological effects associated with difenoconazole and its degradates. It also describes the preliminary ecological risk hypothesis and analysis plan for evaluating and characterizing risk to non-target species in support of the registration review of difenoconazole. This document also recommends studies that should be included in a generic data call-in (DCI) to address uncertainties surrounding the environmental fate and potential ecological effects of difenoconazole.

EFED recommends the following studies to reduce uncertainty in the risk assessment[1]:

- 850.4550: Cyanobacteria toxicity (difenoconazole; TGAI)*
- 850.4100: Terrestrial plant toxicity (seedling emergence) – (TEP)*
  - Tier II testing is required for lettuce, soybean, and sugar beet. A NOAEC must be established at the maximum single application rate (Tier 1 test) for the other seven test species (those showing no effects in the available study, MRID 48453203); alternatively, Tier II testing may be conducted for those species.
- 850.4150 : Terrestrial plant toxicity (vegetative vigor) – (TEP)*
  - A NOAEC must be established for all ten test species at the maximum single application rate (Tier I test). Alternatively, Tier II testing may be conducted.
- Non-guideline: Chronic toxicity to benthic invertebrates (whole sediment; 3 test species: freshwater amphipod, freshwater midge, and estuarine/marine amphipod) – (difenoconazole; TGAI)*
  - EFED recommends that the registrant consider Agency-wide guidelines for chronic testing of freshwater and estuarine/marine organisms[2,3] because the OCSPP 850 series guidelines are in the process of being finalized. A protocol must be submitted for review prior to initiating the studies.
- Non-guideline Tier I: Honeybee adult acute oral exposure (difenoconazole; TGAI)
- Non-guideline Tier I: Honeybee adult chronic oral exposure (difenoconazole; TGAI)
- Non-guideline Tier I: Honeybee larval acute and chronic oral exposure (difenoconazole; TGAI)
- Non-guideline Tier II: Residue in pollen and nectar (recommendation pending risks identified in Tier I studies) (TEP)
- Non-guideline Tier II: semi-field testing for pollinators (tunnel and feeding studies) (recommendation pending risks identified in Tier I studies) (TEP)
- 850.3040: Tier III full-field testing for pollinators (recommendation pending risk identified in Tier II studies) (TEP)
- 850.6100: ILV: Independent laboratory validation report for analytical method in soil for difenoconazole and its metabolites (CGA-205375, CGA-142856, and CGA-71019).
- 850.6100: ECM/ILV: Environmental chemistry method and independent laboratory validation reports for analytical method in water for difenoconazole and its metabolites (CGA-205375, CGA-142856, and CGA-71019).

Toxicity data from other sources (*e.g.*, other conazoles) may be used in the absence of data for difenoconazole. Use of surrogate data may over or underestimate risk of difenoconazole use.

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[1] The studies marked with an asterisk (*) were recently required as a condition of registration for a PRIA label amendment for EPA Reg. No. 100-739 to add new uses to the label for use on Legumes Subgroup 6C and Bushberry Subgroup 13-07B; Related to Petition #4F8231 (May 6, 2015).

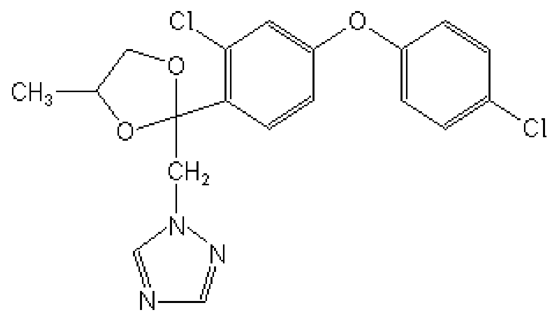
[2] USEPA 2000. Methods for Measuring the Toxicity and Bioaccumulation of Sediment-associated Contaminants with Freshwater Invertebrates. EPA 600/R-99/064

[3] USEPA 2001. Methods for Assessing the Chronic Toxicity of Marine and Estuarine Sediment-associated Contaminants with the Amphipod *Leptocheirus plumulosus*. EPA 600/R-01/020.

EFED recommends the following label changes to reduce uncertainty in the risk assessment:

EFED requests that the registrant provide maximum annual application rates per acre (maximum lb ai/A/year) on all labels in addition to the currently labeled per-crop or per-season rates. Potential accumulation of difenoconazole is a concern given that it is persistent and because many crops may have multiple crop seasons per year. In the absence of labeled maximum annual application rates (or labeled maximum number of crop seasons/year), EFED will assume multiple crop seasons for applicable crops and make conservative assumptions about the number of seasons based on the best available information.

Problem Formulation for the Environmental Fate, Ecological Risk, Endangered Species, and Drinking Water Exposure Assessments in Support of the Registration Review of Difenoconazole



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Environmental Fate and Effects Division
Prepared by:
Michael Lowit, Ph.D., Ecologist
Faruque Khan, Ph.D., Senior Fate Scientist

Reviewed by:
Ryan Mroz, Biologist
Gregory Orrick, RAPL

U.S. Environmental Protection Agency
Office of Pesticide Programs
Environmental Fate and Effects Division
Environmental Risk Branch I
1200 Pennsylvania Ave., NW
Mail Code 7507P
Washington, DC 20460

Table of Contents

1. Purpose

The purpose of this problem formulation is to provide an understanding of what is known about the environmental fate, ecological effects, and currently registered uses of difenoconazole. This document provides a plan for analyzing data relevant to difenoconazole and for conducting environmental fate, ecological risk, endangered species, and drinking water exposure assessments for its registered uses. Additionally, this problem formulation identifies data gaps, uncertainties, and potential assumptions used to address those uncertainties relative to characterizing the potential ecological risk associated with the registered uses of difenoconazole.

2. Problem Formulation

2.1. Nature of Regulatory Action

As part of the implementation of the Registration Review program[4] pursuant to Section 3(g) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), the Agency is beginning its evaluation of difenoconazole to determine whether it continues to meet the FIFRA standard for registration. This problem formulation in support of the Registration Review of difenoconazole will be posted in the initial docket which will be open to the public phase of the review process.

2.2. Previous Assessments

2.2.1. Ecological Risk Assessments

Difenoconazole was first registered in the US in 1994 as systemic broad-spectrum fungicide; it is currently registered for use on a variety of food crops, ornamental plants, and turf. Previous ecological risk assessments (ERA) identified risk concerns primarily for aquatic invertebrates, fish, birds, and mammals on a chronic basis and on an acute basis for estuarine/marine invertebrates for certain uses (*most recent*: USEPA, 2014a). Risk concerns for terrestrial plants were limited to listed dicot species.

2.2.2. Drinking Water Exposure Assessments

The most recent drinking water assessment (DWA) in support of human health risk assessment was conducted in 2014 to support the registration of difenoconazole on numerous uses including artichoke, ginseng, berry and small fruits (subgroup 13-07B), legume vegetables (subgroup 6C) as well as conversion of use on stone fruit to crop group 12-12 and tree nuts to crop group 14-12 (USEPA, 2014b). The estimated drinking water concentrations (EDWCs) of difenoconazole and its major degradate, CGA-205375 (aka, M1), were generated using application rates of 0.46 to 0.52 lb ai/A with the Surface Water Concentration Calculator model (SWCC) for surface water and the maximum application rate of 0.52 lb ai/A with the PRZM-GW and SCI-GROW models for groundwater. For surface water, the EDWCs did not exceed those recommended in the previous DWA for use on grapes (*see* USEPA, 2013), which were a peak (acute) concentration of 20.0 µg/L, an annual mean (non-cancer chronic) concentration of 13.6 µg/L, and a 30-year annual average concentration (cancer chronic) of 9.9 µg/L. PRZM-GW estimated groundwater concentrations were: acute = 1.77 µg/L and chronic = 0.66 µg/L for the maximum application rate of 0.52 lb ai/A for the FL citrus scenario.

[4] http://www2.epa.gov/pesticide-reevaluation/registration-review-process

3. Stressor Source and Distribution

3.1. Mechanism of Action

Difenoconazole is a broad-spectrum triazole fungicide that works by inhibiting demethylation and other processes in sterol biosynthesis. Difenoconazole is a penetrating systemic fungicide which is rapidly absorbed by leaves and is then distributed within plant tissue by translaminar movement.

3.2. Overview of Pesticide Use and Usage

Estimates of the actual usage of difenoconazole on agricultural crops are summarized in **Table 1** (Screening Level Usage Analysis (SLUA) provided by the Biological and Economic Analysis Division (BEAD) on October 2, 2014). Primary uses in terms of average weight of applied product of difenoconazole are wheat (seed treatment), potatoes, and sugar beet. These data represent usage information from 2004 to 2014.

Difenoconazole is labeled for use on a variety of food crops, ornamental plants, and turf. Most uses allow aerial and ground applications and in some cases chemigation. A summary of previously assessed uses, maximum application rates, number of applications, and minimum application intervals is reported in **Appendix A**. The registration review risk assessment will be based on current label information at the time of assessment as provided by BEAD.

To reduce uncertainty in the risk assessment, EFED requests that the registrant provide annual maximum application rates per acre (maximum lb ai/A/year) on all labels in addition to the currently labeled per-crop or per-season rates that remain on some labels. Potential accumulation of difenoconazole is a concern given that it is persistent and because many crops may have multiple crop seasons per year. In the absence of labeled maximum annual application rates (or labeled maximum numbers of crop seasons/year), EFED will assume multiple crop seasons for applicable crops and make conservative assumptions about the number of seasons based on best available information.

Table 1. Estimated Usage of Difenoconazole on Agricultural Crops

Crop	Average Annual Usage lb ai/A	Percent (%) Crop Treated	
		Average	Maximum
Almonds	7,000	5	15
Apples	7,000	15	25
Brussels Sprouts[1]	<500	Not calculated	
Cabbage	<500	<2.5	5
Cantaloupes	<500	<2.5	<2.5
Cucumbers	3,000	5	10
Garlic	<500	5	5
Grapefruit	<500	<2.5	<2.5
Grapes	9,000	5	10
Onions	2,000	5	10
Oranges	1,000	<2.5	<2.5

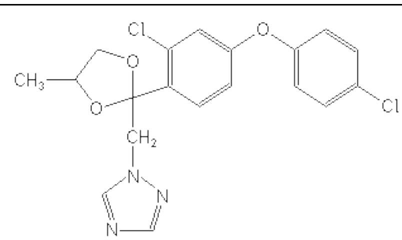
Crop	Average Annual Usage lb ai/A	Percent (%) Crop Treated	
		Average	Maximum
Peaches	<500	<1	<2.5
Pears	<500	5	10
Pecans	1,000	<2.5	<2.5
Peppers	<500	<2.5	5
Pistachios	<500	<2.5	5
Potatoes	20,000	15	30
Pumpkins	<500	<2.5	5
Squash	<500	5	10
Strawberries	<500	<2.5	<2.5
Sugar Beets	20,000	15	30
Tangerines	1,000	<2.5	<2.5
Tomatoes	7,000	25	40
Walnuts	<500	<2.5	<2.5
Watermelons	2,000	5	10
Wheat (Seed Treatment)	40,000	10	15

[1] Based on CA DPR data only (80% or more of U.S. acres grown are in California)

3.3. Physical, Chemical, and Environmental Fate Properties of Difenoconazole and its Degradates

Difenoconazole is a water soluble (15 mg/L) chemical. It has a relatively low vapor pressure (2.5×10^{-10} mm Hg) and Henry's Law constant (8.9×10^{-12} atm·m3/mol), which suggest that volatilization is not expected to be a major route of dissipation from soil and water. Select physical and chemical properties are presented in **Table 2**.

Table 2. Physical and Chemical Properties of Difenoconazole

Property	Value	Source
Common Name	Difenoconazole	MRID 46950104
CAS Registry No.	119446-68-3	
PC Code	128847	
Structure		
Chemical Name (CAS)	1-{2-[4-(chlorophenoxy)-2-chlorophenyl-(4-methyl - 1,3-dioxolan-2-yl)-methyl]} -1H-1,2,4-triazole	

Property	Value	Source
SMILES notation	O1CC(C)OC1(Cn2ncnc2)c3c(Cl)cc(Oc4ccc(Cl)cc4)cc3	EPI Suite, v3.12 SMILES
Molecular Formula	$C_{19}H_{17}Cl_2N_3O_3$	MRID 46950104
Molecular Weight	406.27	
Physical State	Red Liquid	
Vapor pressure	2.5 x 10^{-10} mm Hg (25 ^oC)	MRID 46515901
Henry's Law constant	8.9 x 10^{-12} atm x m^3/mol	MRID 46515901
Specific Gravity/ Density	1.14g/cm^3 @ 25 ^oC	MRID 46950104
Solubility in water	15.0 mg/L @ 25 ^oC	MRID 46950104
log K_{ow}	4.4 (25 ^oC)	MRID 46950105

Table 3 summarizes the environmental fate data for difenoconazole. Difenoconazole was stable to hydrolysis at pH 5, 7, and 9 in aqueous buffered solutions. Aqueous photolysis half-lives ranged from 9.2 to 228 days in sterile buffer solutions. Difenoconazole may potentially undergo relatively fast photolysis (DT_{50} of 6 days) in natural aquatic environments, which may be attributable to indirect photolysis via irradiation absorption by organic components present in the natural water. However, difenoconazole was stable to soil photolysis.

Difenoconazole is relatively stable to aerobic and anaerobic soil metabolism and aerobic and anaerobic aquatic metabolism. When applied at 0.1-0.23 ppm to a variety of European and domestic aerobic soils, difenoconazole degraded with half-lives ranging from 84.5 to 533 days. At a concentration of 10 ppm in a loam soil, difenoconazole degraded with half-lives of 1059 to 1600 days under aerobic conditions and 947 days under anaerobic conditions.

In aquatic environments under aerobic conditions, difenoconazole degraded with half-lives ranging from 315 to 565 days at concentrations up to 0.17 g ai/L and 860 days at a concentration of 10 mg ai/L. Under anaerobic conditions, difenoconazole degraded with half-lives of 370 days at a concentration of 0.04 mg ai/L and 1245 days at a concentration of 10 mg ai/L. The longer half-life values obtained in both terrestrial and aquatic environments with higher concentrations may imply that the rate of microbially mediated degradation of difenoconazole may be concentration dependent.

During aqueous photolysis, difenoconazole breaks down to 1,2,4-triazole acetic acid (aka, triazole acetic acid and CGA-142856) and is further degraded to triazole methanol (aka, CGA-107069), and 1,2,4-triazole (aka, CGA-71019). In aerobic soil, difenoconazole degrades slowly to the ketone CGA-205374, which in turn is reduced to the alcohol CGA-205375, the cleavage product 1,2,4-triazole, carbon dioxide, and minor compounds. CGA-205375 and 1,2,4-triazole were also identified as degradates in aerobic and anaerobic metabolism studies. CGA-205375 consistently reached a maximum of 4.4% to 14.8% in biodegradation studies. The greatest formation of 1,2,4-triazole was observed in the anaerobic aquatic metabolism study (35.9% at study termination; 350 days). Triazole acetic acid reached a maximum of 42% at the end of the aquatic photolysis study (30 days) and CGA-205375 was detected at a maximum of 14% at the end of terrestrial field study (580 days). The non-extractable fraction (8.1% to 48.9%) was a major sink for the applied difenoconazole, while mineralization accounted for 0.6% to 23.4% AR in laboratory aerobic and anaerobic metabolism studies. Chemical names, structures, and formation of major and minor degradates are reported in **Appendix B**.

Submitted terrestrial field dissipation studies showed that difenoconazole and its degradates did not leach below 30 cm of soil depth except in one study where leaching was noted up to 60 cm of the cropped plot soil (under potato production conditions in ND; MRID 46950129). Difenoconazole dissipated with half-lives ranging from 136 to 462 days in the terrestrial field dissipation studies.

Difenoconazole appears to be slightly mobile to hardly mobile in soils (FAO, 2000). Freundlich adsorption coefficient ($K_{F(ads)}$) values were 12.8 mL/g for sand soil, 63.0 mL/g for sandy loam soil, 54.8 mL/g for silt loam soil, and 47.2 mL/g for silty clay loam soil. The corresponding K_{Foc} values were 3867, 3518, 3471, and 7734 mL/g. $K_{F(ads)}$ values for difenoconazole are directly proportional to the soil organic carbon content. In another study, $K_{F(ads)}$ values were 11.6, 22.9, 182, and 201 mL/g for the Madera loamy sand, Visalia sandy loam, North Dakota clay loam, and Florida sand soils, respectively; corresponding K_{Foc} values were 3870, 4587, 4799, and 11202 mL/g. However, this study was conducted with autoclaved soil, potentially distorting the mobility characteristics of difenoconazole.

The octanol water partition coefficient (log Kow of 4.4) suggests that difenoconazole has a potential to bioaccumulate. Difenoconazole accumulated rapidly in edible and non-edible bluegill sunfish tissues with bioconcentration factors of 170x for edible tissues, 570x for non-edible tissues, and 330x for whole body. Depuration was also rapid with a depuration half-life of approximately 1 day and 96-98% clearance after 14 days of depuration. One metabolite, CGA-205375, was recovered from both edible and non-edible tissues, accounting for 51-64% of the applied difenoconazole.

Table 3. Summary of the Environmental Fate Properties of Difenoconazole

Property	Value	Source
Hydrolysis half-life pH = 5 pH = 7 pH = 9	 Stable Stable Stable	 MRID 42245127
Photolysis half-life in water	6 days – ca. 1 ppm in in natural water ca. 9.2 days – 1mg ai/L sterile buffer solution 228 days – 1.52 mg ai/L in sterile buffer solution (15-day study) <u>Major degradates (maximum % [at day])</u> CGA-142856 (41.8 [30d]) CGA-107069 (12.27 [30d]) 1,2,4-triazole (12.9 [9d])	MRID 42245128 MRID 46950104 MRID 46950105
Photolysis half-life in soil	349 - 823 days[1] No major degradates	MRID 469501-06 & -07[3]

Property	Value	Source
Aerobic soil metabolism half-life	84.5 days – at 0.1 ppm concentration 1600 days – at 10 ppm in loam[2] 1059 days – at 10 ppm in sandy loam[2] 120 days – at 0.13 ppm; Swiss loam 104 days – at 0.13 ppm; Swiss loam 158 days – at 0.23 ppm; Swiss sandy loam 187 days – at 0.23 ppm; Swiss sandy loam/loamy sand 198 days – at 0.23 ppm; French silty clay loam 408 days – at ca. 0.1 ppm in CA loamy sand at 25ºC 533 days – at ca. 0.1 ppm in CA loamy sand at 25ºC <u>Major degradates (maximum % [at day])</u> CGA-205375 (14.8 [360d] 1,2,4-triazole (20.6 [190d]) Non-extractable residue (48.9 [293d])	MRID 42245131 MRID 42245132 MRID 42245133 MRID 46950109 MRID 46950110 MRID 46950111 MRID 469501-12 & -13 MRID 469501-14 & -15
Anaerobic soil metabolism half-life	947 days – at 10 ppm in loam[2] No major degradates	MRID 42245132
Aerobic aquatic metabolism half-life	860 days (10 mg ai/L)[2]; rice paddy water 330 days (0.17 mg ai/L); Swiss pond water-silty clay loam sediment 301 days; Swiss river water-sandy loam sediment 565 days; water and loamy sand sediment from river near Porterville, CA <u>Major degradate (maximum % [at day])</u> CGA-205375 (11.6 [90d]) Non-extractable residue (8.9 [112d])	MRID 42245134 MRID 46950116 MRID 469501-17 &-18
Anaerobic aquatic metabolism half-life	1245 days (10 mg ai/L)[2]; rice paddy water 433 days (0.04 mg ai/L); water and loamy sand sediment from river near Porterville, CA <u>Major degradates (maximum % [at day])</u> CGA-205375 (12.6 [175d] CGA-71019 (35.9 [350d]) Non-extractable residue (8.1 [302d])	MRID 42245134 MRID 469501-19 & -20
Terrestrial field dissipation half-life	252 days - determined in the 0- to 3-inch depth – CA bare loamy sand 231 days – GA bare loamy sand (four applications of 0.13 lb ai/A) 139 days – CA bare plot of loam soil (four applications of 0.13 lb ai/A) 462 days – ND bare sandy clay loam No major degradates	MRID 42245140 MRID 46950126 MRID 46950127 MRID 46950129

Property	Value	Source
Soil adsorption coefficient $K_{F(ads)}$ and K_{Foc} (L/kg)	$K_{F(ads)}$ and (1/n) soil 11.61 (0.80) Madera loamy sand 22.94 (0.84) Visalia sandy loam 182.4 (0.86) North Dakota clay loam 201.6 (0.91) Florida sand K_{Foc} (% of organic carbon) soil 3870 (0.3) Madera loamy sand 4587 (0.5) Visalia sandy loam 4799 (3.8) North Dakota clay loam 11202 (1.8) Florida sand	MRID 469501-21 & -22
	$K_{F(ads)}$ and (1/n) soil 12.8 (0.74) Sand 63.0 (0.76 Sandy loam 54.8 (0.85) Silt loam 47.2 (0.91) Silty clay loam K_{Foc} (% of organic carbon) soil 3867 (0.33) Sand 3518 (1.79) Sandy loam 3471 (1.58) Silt loam 7734 (0.61) Silty clay loam	MRID 42245135[3]
	CGA-205375 $K_{F(ads)}$ and (1/n) soil 9.64 (0.83) Madera loamy sand 12.35 (0.83) Visalia sandy loam 145.32 (0.73) North Dakota clay loam 115.77 (0.84) Florida sand K_{Foc} (% of organic carbon) soil 3214 (0.3) Madera loamy sand 2470 (0.5) Visalia sandy loam 3824 (3.8) North Dakota clay loam 6432 (1.8) Florida sand	MRID 469501-23 & -24
Bluegill sunfish (*Lepomis macrochirus*) bioconcentration (BCF) factor Depuration half-life	170x in edible tissues 570x nonedible tissues 330x for whole body 1 day	MRID 46950123

[1] The soil photolysis half-life under xenon light conditions was recalculated to represent the conditions under natural sunlight intensity during 30-day periods between June and September (104.7-246.9 W·min/cm^2), as a result, a range of half-lives was obtained.
[2] The test application rate was significantly higher than expected under registrant-proposed use conditions for difenoconazole.
[3] The test soils were autoclaved prior to conducting the study which could distort the mobility characteristic of difenoconazole, thus, the study results will not be used as modeling input parameters.

Major degradates (CGA-205375, 1,2,4 triazole, and triazole acetic acid)

There are few environmental fate studies available for the major degradates of difenoconazole. CGA-205375 has the potential to be slightly more mobile (FAO, 2000) in the soil than the parent compound. Freundlich adsorption values for CGA-205375 are 9.6, 12.3, 145, and 116 mL/g for the Madera loamy sand, Visalia sandy loam, North Dakota clay loam, and Florida sand soils, respectively; corresponding K_{Foc} values are 3214, 2470, 3824, and 6432 mL/g. In addition, the $K_{F(ads)}$ values for CGA-205375 are directly proportional to soil organic carbon content.

The environmental fate properties of 1,2,4-triazole and triazole acetic acid were provided in a recent registration review problem formulation for myclobutanil (*see* USEPA, 2015). Abiotic (hydrolysis half-lives = 99 to 421 days; stable to aqueous photolysis) and biotic degradations are not major routes of 1,2,4-triazole degradation. Microbial degradation of 1,2,4-triazole in aerobic soils is highly varied (half-lives = 20 days to stable). 1,2,4-triazole is moderately persistent in anaerobic soil (half-life = 81 days). The major transformation products of 1,2,4-triazole are triazole acetic acid and hydroxytriazole. Both transformation products are formed through microbial degradation in aerobic soils.

3.4. Monitoring Data

EFED is aware of monitoring data for difenoconazole. Available data from sources including federal and state agencies will be considered in the DWA and ERA.

3.5. Clean Water Act

Difenoconazole is not identified as a cause of impairment for any water bodies listed as impaired under section 303(d) of the Clean Water Act.[5] In addition, no Total Maximum Daily Loads (TMDL) have been developed.[6] The Impaired Waters and Total Maximum Daily Loads website can be consulted for more information.[7] The Agency invites submission of water quality data for difenoconazole. To the extent possible, data should conform to the quality standards in the *OPP Standard Operating Procedure: Inclusion of Impaired Water Body and Other Water Quality Data in OPP's Registration Review Risk Assessment and Management Process*[8], in order to ensure they can be used quantitatively or qualitatively in pesticide risk assessments.

4. Receptors

Consistent with the process described in the Overview Document (USEPA, 2004), the risk assessment for difenoconazole relies on a surrogate species approach. Toxicological data generated from surrogate test species, which are intended to be representative of broad taxonomic groups, are used to extrapolate the potential effects on a variety of species (receptors) included under these taxonomic groupings.

Acute and chronic toxicity data from studies submitted by pesticide registrants along with the available open literature will be used to evaluate the potential direct and indirect effects of difenoconazole to aquatic and terrestrial receptors. This includes toxicity on the technical grade active ingredient, degradates, and when available, formulated products (*e.g.*, "Six-Pack" studies). Open literature studies will be identified through EPA's ECOTOXicology (ECOTOX) database[9], which employs a literature search engine for locating chemical toxicity data.

A summary of available toxicity data representing non-target organisms exposed to difenoconazole and major degradates (1,2,4-triazole, triazole acetic acid, and CGA-205375) is

[5] http://iaspub.epa.gov/tmdl_waters10/attains_nation_cy.cause_detail_303d?p_cause_group_id=885
[6] http://iaspub.epa.gov/tmdl_waters10/attains_nation.tmdl_pollutant_detail?p_pollutant_group_id=885&p_pollutant_group_name=PESTICIDES
[7] http://www.epa.gov/owow/tmdl/
[8] http://archive.epa.gov/pesticides/ppdc/ppdc/2006/november06/session1-sop.pdf
[9] http://cfpub.epa.gov/ecotox/

provided in **Sections 4.1**, **4.2, 4.3,** and **4.4**. Ecological Structure Activity Relationship (ECOSAR) methods[10] were used to estimate toxicity of the major degradates in cases where data are unavailable; results are discussed below and are presented in **Appendix C**. A review of ecological incidents associated with difenoconazole is provided in **Section 4.5**. The ECOTOX database will be searched when the risk assessment for difenoconazole is prepared. At that time, EFED will review the endpoints from open literature studies that are more sensitive than those from available guideline studies.

4.1. Toxicity of Difenoconazole

Table 4. Summary of Aquatic Taxa Toxicity Endpoints for Difenoconazole

Type of Study	Species	Toxicity Value (µg ai/L)	MRID
Acute – Freshwater Fish	Rainbow trout (*Oncorhynchus mykiss*)	96-hr LC_{50} = 810 (630-1200)[1] NOAEC = 350 LOAEC = 630 based on mortality, darkened pigmentation, and lethargy Other sublethal effects: decreased respiration --- 96-hr LC_{50} = 1060 (970-1130)[1] Slope = 16.1 (9.0-23.3) NOAEC < 580 LOAEC ≤ 580 based on partial loss of equilibrium and lethargy Other sublethal effects: darkened pigmentation	42245107 ------------------ 42245108
	Bluegill Sunfish (*Lepomis macrochirus*)	96-hr LC_{50} = 1200 (900-1700)[1] NOAEC = 520 LOAEC = 900 based on surfacing, loss of equilibrium, fish on the bottom, and quiescence	42245109
	Fathead minnow (*Pimephales promelas*)	96-hr LC_{50} = 1800 (1300-2600)[1] NOAEC = 660 LOAEC = 1300 based on mortality, lethargy, and loss of equilibrium Other sublethal effects: lying on the bottom or surface	48453201

[10] ECOSAR predictive software is available publically though the Epi Suite™ program. http://www2.epa.gov/tsca-screening-tools/ecological-structure-activity-relationships-ecosar-predictive-model

Type of Study	Species	Toxicity Value (µg ai/L)	MRID
Chronic – Freshwater Fish	Fathead minnow (*Pimephales promelas*)	*Early Life Stage* NOAEC = 8.7 LOAEC = 19 based on reduced larval length 30-days post-hatch --- *Life Cycle* NOAEC = 1.9 LOAEC = 3.7 based on reduced male length of F0-generation 12 weeks post-hatch	42245115 ------------------ 48453205
	Rainbow trout (*Oncorhynchus mykiss*)	NOAEC = 0.86 Value used for risk assessment. Based on acute-to-chronic ratio of fathead minnow data to rainbow trout data (the most acutely sensitive species).[2]	-
Acute – Freshwater Invertebrate	Water flea (*Daphnia magna*)	48-hr EC_{50} = 770 (590-950) [1] Slope = 4.1 (2.5-5.7) [1] NOAEC < 520 LOAEC ≤ 520 based on mortality Other sublethal effects: on bottom and quiescence	42245110
Chronic – Freshwater Invertebrate	Water flea (*Daphnia magna*)	NOAEC = 5.6 LOAEC = 13.0 based on reduced number of young/adult/reproductive day and adult length	42245114
Chronic – Freshwater Invertebrate (Sediment)	Midge (*Chironomus riparius*)	NOAEC = 5 mg ai/kg-sediment LOAEC = 50 mg ai/kg-sediment based on emergence rate & development rate	47648601[3]
Acute – Estuarine/Marine Fish	Sheepshead minnow (*Cyprinodon variegates*)	96-hr LC_{50} = 819 (0-infinity)[1] NOAEC = 325 LOAEC = 428 based on mortality Other sublethal effects: lethargy and lying on the bottom --- 96-hr LC_{50} = 1100 (900-1500)[1] NOAEC = 270 LOAEC = 400 based on loss of equilibrium	42245112 ------------------ 42906702

Type of Study	Species	Toxicity Value (µg ai/L)	MRID
Chronic – Estuarine/Marine Fish	Sheepshead minnow (*Cyprinodon variegates*)	NOAEC = 0.86 Based on acute-to-chronic ratio of fathead minnow data to sheepshead minnow data.[4]	-
Acute – Estuarine/Marine Mollusk	Eastern oyster (*Crassostrea virginica*)	96-hr EC_{50} = 424 (333-539)[1] NOAEC = 180 LOAEC = 340 based on reduced shell growth --- 96-hr EC_{50} > 300 NOAEC = 210 LOAEC = 300 based on reduced shell growth	42906701 ------------------ 42245113
Acute – Estuarine/Marine Invertebrate	Mysid shrimp (*Americamysis bahia*)	96-hr LC_{50} = 150 (125-193)[1] Slope = 4.7 (2.7-6.7) [1] NOAEC = 480 LOAEC = 730 based on mortality	42245111
Chronic – Estuarine/Marine Invertebrate	Mysid shrimp (*Americamysis bahia*)	NOAEC < 0.115 LOAEC ≤ 0.115 based on reduced number of young/adult/reproductive day --- NOAEC < 0.31 LOAEC ≤ 0.31 based on reduced number of young/adult/reproductive day and number of young/adult --- NOAEC = 4.8 LOAEC = 10 based on reduced F0 post-pairing survival, offspring/female and time to first brood	46950133 ------------------ 47648603 ------------------ 49322901 and 49387801
Vascular Plant – Freshwater	Duckweed (*Lemna gibba*)	7-day EC_{50} = 1900 (1600-2400)[1,5] Slope = 1.3±0.9[6] EC_{05} = 110 (59-190) [1] NOAEC < 110 LOAEC ≤ 110 based on reduced frond number	46950204

Type of Study	Species	Toxicity Value (µg ai/L)	MRID
Non-vascular Plant	Freshwater Diatom (*Navicula pelliculosa*)	96-hr EC_{50} = 98 (68-140) [1,5] Slope = 2.3±0.3 (poor fit)[6] NOAEC = 53 LOAEC = 150 based on reduced cell density	46950208
	Freshwater Algae (*Pseudokirchneriella subcapitata)*	96-hr EC_{50} = 300 (200-440) [1,5] Slope = 2.9±0.5 (poor fit)[6] NOAEC = 150 LOAEC = 360 based on reduced cell density	46950212
	Marine Diatom (*Skeletonema costatum)*	96-hr EC_{50} = 430 (300-630) [1,5] Slope = 2.4±0.4[6] EC_{05} = 87 (39-190)[1] NOAEC < 6.3 LOAEC ≤ 6.3 based on reduced cell density	46950210

[1] Range is 95% confidence interval.
[2] Acute toxicity to fathead minnow: LC_{50} = 1800 µg ai/L (MRID 48453201); acute toxicity to rainbow trout: LC_{50} = 810 µg ai/L (MRID 42245107), and chronic toxicity to fathead minnow: NOAEC = 1.9 µg ai/L (MRID 48453205)
[3] This is a range finding study and should not be used quantitatively for risk assessment.
[4] Acute toxicity to fathead minnow: LC_{50} = 1800 µg ai/L (MRID 48453201); acute toxicity to sheepshead minnow: LC_{50} = 819 µg ai/L (MRID 42245112), and chronic toxicity to fathead minnow: NOAEC = 1.9 µg ai/L (MRID 48453205)
[5] Most sensitive endpoint (based on EC_{50}) is reported.
[6] ± standard error

Table 5. Summary of Terrestrial Taxa Toxicity Endpoints for Difenoconazole

Type of Study	Species	Toxicity Value	MRID
Acute – Avian Oral Dose	Canary (*Serinus canaria*)	LD_{50} > 2000 mg ai/kg-bw NOAEL ≥ 2000 mg ai/kg-bw LOAEL > 2000 mg ai/kg-bw	48453202
	Mallard duck (*Anas platyrhynchos*)	LD_{50} > 2150 mg/kg-bw NOAEL < 2150 mg/kg-bw LOAEL ≤ 2150 mg/kg-bw based on reduced body weight gain and feeding	42245105
Acute – Avian Dietary	Bobwhite quail (*Colinus virginianus*)	LC_{50} = 4760 mg/kg-diet (4103-5522) [1] Slope = 1.2 NOAEC = 625 mg/kg-diet LOAEC = 1250 mg/kg-diet based on reduced body weight and feeding	42245103
	Mallard duck (*Anas platyrhynchos*)	LC_{50} > 5000 mg/kg-diet NOAEC = 625 mg/kg-diet LOAEC = 1250 mg/kg-diet based mortality Other sublethal effects: reduced body weight and feeding	42245104
Chronic – Avian Dietary	Bobwhite quail (*Colinus virginianus*)	NOAEC = 21.9 mg ai/kg-diet LOAEC = 108 mg ai/kg-diet based on reduction in hatchling body weight	46950202

Type of Study	Species	Toxicity Value	MRID
Chronic – Avian Dietary	Mallard duck (*Anas platyrhynchos*)	NOAEC = 110.8 mg ai/kg-diet LOAEC = 492.9 mg ai/kg-diet based on egg shell thinning	42245106
Acute – Mammalian Oral Dose	Laboratory rat (*Rattus norvegicus*)	LD_{50} = 1453 mg ai/kg-bw	42090006
Two Generation Reproduction – Mammalian	Laboratory rat (*Rattus norvegicus*)	NOAEC = 25 mg ai/kg-diet LOAEC = 250 mg ai/kg-diet based on reduced maternal body weight gain and reduced pup weight	42090018
Acute Contact – Terrestrial Invertebrate	Honey bee (*Apis mellifera*)	LD_{50} >100 µg ai/bee NOAEL ≥ 100 µg ai/bee LOAEL > 100 µg ai/bee	42245124
Acute Contact – Terrestrial Invertebrate	Earthworm (*Eisenia fetida*)	14-day LC_{50} > 610 mg ai/kg-dw soil NOAEC ≥ 610 mg ai/kg-dw soil LOAEC > 610 mg ai/kg-dw soil	42245125
Tier I – Terrestrial Plants	Corn, Onion, Ryegrass, Wheat, Radish, Cabbage, Lettuce, Sugar beet, Soybean, and Tomato	*Seedling Emergence* EC_{25} > 0.111/0.112 lb ai/A[2] NOAEC < 0.111/0.112 lb ai/A[2,3] LOAEC ≤ 0.111/0.112 lb ai/A[2,3] --- *Vegetative Vigor* EC_{25} > 0.123 lb ai/A NOAEC ≥ 0.123 lb ai/A LOAEC > 0.123 lb ai/A	48453203 ------------------ 48453204

[1] Range is 95% confidence interval.
[2] Some species were exposed to 0.111 lb ai/A and others were exposed to 0.112 lb ai/A.
[3] Effects at 0.11 lb ai/A on lettuce, sugar beet, and soybean were considered biologically significant. Lettuce showed reduced emergence (21%), survival (17%), shoot length (26%), and dry weight (24%). Soybean showed reduced shoot length (23%). Sugar beet showed reduced survival (18%).

4.2. Toxicity of 1,2,4-Triazole (PC 600074)

Available guideline data for 1,2,4-triazole are presented in **Table 6** and **7**. 1,2,4-triazole is less toxic than difenoconazole to non-vascular plants (green algae), freshwater fish (acute basis), and freshwater invertebrates (acute basis). In contrast, birds are more acutely sensitive to 1,2,4-triazole compared to difenoconazole. Finally, both 1,2,4-triazole and difenoconazole showed chronic effects to mammals at 250 mg ai/kg-diet; however, there is uncertainty about the relative chronic toxicity of the two compounds because a NOAEC was established in the difenoconazole study (25 mg ai/kg-diet) whereas the 1,2,4-triazole study did not test below 250 mg ai/kg-diet.

Non-guideline, summary report data on acute oral toxicity to rats (MRID 45284001, 45284004, and 45284008) suggests that 1,2,4-triazole (LD_{50}s ranging from 1375 to 3080 mg/kg-bw) and difenoconazole (LD_{50} = 1453 mg ai/kg-bw) are equally as toxic.

Table 6. Summary of Aquatic Taxa Toxicity Endpoints for 1,2,4-Triazole

Type of Study	Species	Toxicity Value (µg ai/L)	MRID
Acute – Freshwater Fish	Rainbow trout (*Oncorhynchus mykiss*)	96-hr LC_{50} = 498,000	48474301

Type of Study	Species	Toxicity Value (µg ai/L)	MRID
Acute – Freshwater Invertebrate	Water flea (*Daphnia magna*)	48-hr EC_{50} > 98,100	48453206
Non-vascular Plant	Freshwater Algae (*Pseudokirchneriella subcapitata)*	96-hr EC_{50} = 14,000	45880401

Table 7. Summary of Terrestrial Taxa Toxicity Endpoints for 1,2,4-Triazole

Type of Study	Species	Toxicity Value	MRID
Acute – Avian Oral Dose	Bobwhite quail (*Colinus virginianus*)	LD_{50} = 770 mg ai/kg-bw	49380701
Two Generation Reproduction – Mammalian	Laboratory rat (*Rattus norvegicus*)	NOAEC < 250 mg ai/kg-diet LOAEC ≤ 250 mg ai/kg-diet based on reduced body weight and body weight gain in F1 males, reduced spleen weight in F1 females and F2 female pups, and reduced body weight, body weight gain, and brain weight in F2 pups	46467304
Subchronic (28 day adult) and reproductive (additional 28 day offspring) – Terrestrial Invertebrate	Earthworm (*Eisenia fetida*)	LC_{50} > 70.81 µg/kg NOAEC ≥ 70.81 µg/kg LOAEC > 70.81 µg/kg	45880402
28 day – Terrestrial Invertebrate	Springtails (*Folsomia candida*)	28-day LC_{50} > 10 mg ai/kg soil NOAEC = 1.8 mg ai/kg soil LOAEC = 3.2 mg ai/kg soil based on reduced number of juveniles	45880404

ECOSAR methods were used to predict chronic toxicity of 1,2,4-triazole to fish and aquatic invertebrates based on its structural similarity to chemicals for which aquatic toxicity data are known (**Appendix C**). Estimates were available for freshwater organisms but not marine/estuarine organisms. A comparison of 1,2,4-triazole ECOSAR estimates to experimentally derived difenoconazole toxicity values suggests that 1,2,4-triazole is much less toxic (two orders of magnitude) than difenoconazole on a chronic basis to freshwater invertebrates and fish. There is reasonable confidence in the ECOSAR estimates for 1,2,4-triazole (at least for fish and non-vascular plants[11]) given that the ECOSAR estimates are within an order of magnitude of the available experimentally derived values.

4.3. Toxicity of Triazole Acetic Acid (PC 600082)

Available guideline data for triazole acetic acid are presented in **Table 8** and **9**. Triazole acetic acid is less acutely toxic than difenoconazole to mammals, freshwater fish, and freshwater invertebrates. It is uncertain if triazole acetic acid is more or less acutely toxic to birds than difenoconazole because none of the available studies for either chemical showed treatment-related mortality up to the highest doses tested (ca. 2000 mg ai/kg-bw).[12]

[11] There is no basis for judging confidence in the ECOSAR estimate of acute toxicity to freshwater invertebrates due to a non-definitive endpoint.
[12] There was one mortality in the canary study (MRID 48453202) that may not have been treatment related.

Table 8. Summary of Aquatic Taxa Toxicity Endpoints for Triazole Acetic Acid

Type of Study	Species	Toxicity Value (µg ai/L)	MRID
Acute – Freshwater Fish	Rainbow trout (*Oncorhynchus mykiss*)	96-hr LC_{50} > 101,000	48453209
Acute – Freshwater Invertebrate	Water flea (*Daphnia magna*)	48-hr EC_{50} > 108,000	48453208

Table 9. Summary of Terrestrial Taxa Toxicity Endpoints for Triazole Acetic Acid

Type of Study	Species	Toxicity Value	MRID
Acute – Avian Oral Dose	Bobwhite quail (*Colinus virginianus*)	LD_{50} > 1926 mg ai/kg-bw	49412601
Acute – Mammalian Oral Dose	Laboratory rat (*Rattus norvegicus*)	LD_{50} > 5000 mg ai/kg-bw	45596802

A comparison of triazole acetic acid ECOSAR estimates to experimentally derived difenoconazole toxicity values suggests that triazole acetic acid is much less toxic (three or more orders of magnitude) than difenoconazole to aquatic non-vascular plants, freshwater fish (chronic basis), and freshwater invertebrates (chronic basis) (**Appendix C**). Estimates were not available for marine/estuarine organisms. There is no basis for judging confidence in the ECOSAR estimates because the ECOSAR estimates for acute toxicity to fish and invertebrates are substantially greater (less toxic) than the non-definitive endpoints observed in the available acute toxicity studies.

4.4. Toxicity of CGA-205375

On an acute oral basis, CGA-205375 and difenoconazole are of similar toxicity to mammals (**Table 5 and 10**).

Table 10. Summary of Terrestrial Taxa Toxicity Endpoints for CGA-205375

Type of Study	Species	Toxicity Value	MRID
Acute – Mammalian Oral Dose	Mouse	LD_{50} = 2309 mg ai/kg-bw[1]	46950303

[1] LD_{50} = 1289 mg ai/kg-bw scaled to laboratory rat weight (350 g) based on an average mouse body weight of 34 g in this study and the following equation: mouse LD_{50} * (mouse bw/rat bw)$^{0.25}$

A comparison of CGA-205375 ECOSAR estimates to experimentally derived difenoconazole toxicity values suggests that CGA-205375 is not more toxic than difenoconazole to aquatic organisms in general and is similar in toxicity (< 10 times difference) to aquatic non-vascular plants, fish (acute basis), and invertebrates (acute basis) (**Appendix C**). The available information also suggests that CGA-205375 and difenoconazole are similar in chronic toxicity to freshwater fish and invertebrates based on ECOSAR estimates of both compounds (< 10 times difference) and to a lesser extent when based on comparison of CGA-205375 ECOSAR estimates to experimentally derived difenoconazole data. Experimentally derived CGA-205375 data are not available to judge the level of confidence in the ECOSAR estimates.

4.5. Incident Databases Review

Reviews were conducted of the Ecological Incident Information System (EIIS, version 2.1.1)[13], the Agency's Aggregated Incidents Reports database, and the Avian Incident Monitoring System (AIMS)[14] on 7/16/2015. No incidents were reported in EIIS or AIMS. Ten minor plant damage incidents were reported for one difenoconazole product (Revus Top) in the aggregated incident database. The Revus Top label indicates that it is a dual ai product containing mandipropamid, a fungicide, as well as difenoconazole.

The total number of actual incidents associated with the use of difenoconazole may be higher than what is reported to the Agency. Incidents may go unreported since effects may not be immediately apparent or readily attributed to the use of a chemical. As such, the absence of incident reports cannot be construed as the absence of incidents.

5. Exposure Pathways of Concern

The use patterns and environmental fate properties of difenoconazole indicate that exposure to non-target aquatic and terrestrial organisms may occur from direct spray and offsite movement via spray drift and runoff.

An additional exposure pathway that will be considered is the consumption of contaminated fish by piscivorus animals because fate data (log Kow) of difenoconazole (4.4) and CGA-205375 (3.79; EPISUITE estimate) suggest the potential for bioaccumulation of both compounds in the aquatic food web.

<u>Screening Imbibition Program</u>

The Screening Imbibition Program (SIP v.1.0)[15] was used to calculate an upper-bound estimate of bird and mammal exposure to difenoconazole in drinking water. Drinking water exposure alone was determined not to be a potential acute concern for birds or mammals; however, the screen suggests that there is a potential chronic concern for birds and mammals. **Appendix D** provides model results.

<u>Screening Tool for Inhalation Risk</u>

The Screening Tool for Inhalation Risk (STIR v.1.0)[15] was used to provide an upper-bound estimate of exposure of birds and mammals to pesticides through inhalation of spray drift or vapor. The screening suggests that difenoconazole exposure is not likely significant enough for an inhalation risk concern. **Appendix E** provides model results.

6. Analysis Plan

In order to address the risk hypothesis, the potential for adverse effects on the environment is estimated. The use, environmental fate, and ecological effects of difenoconazole will be

[13] http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/technical-overview-ecological-risk-assessment-risk
[14] http://www.abcbirds.org/abcprograms/policy/toxins/aims/aims/index.cfm
[15] http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/models-pesticide-risk-assessment

characterized and integrated to assess risk. This will be accomplished using a risk quotient (RQ; ratio of exposure concentration to effects concentration) approach. Although risk is often defined as the likelihood and magnitude of adverse ecological effects, the risk quotient-based approach does not provide a quantitative estimate of likelihood or magnitude of an adverse effect. However, as outlined in the Overview Document (USEPA, 2004), the likelihood of effects to individual organisms from particular uses of difenoconazole will be estimated using the probit dose-response slope and either the level of concern or actual calculated risk quotient value.

This analysis plan will be revisited and may be revised depending upon a full review of the data available in the open literature and the information submitted by the public in response to the opening of the Registration Review docket.

6.1. Stressors of Concern

Ecological Risk Assessment

Difenoconazole and CGA-205375 will be considered stressors of concern in the difenoconazole ERA. Available information suggests that CGA-205375 and difenoconazole are of similar toxicity. Equal toxicity of difenoconazole and CGA-205375 will be assumed in the absence of data. The other two major degradates, 1,2,4-triazole and triazole acetic acid, will also be considered stressors of concern; however, on a case by case basis. Available information suggests that they are equally as toxic as difenoconazole (*e.g.*, 1,2,4-triazole acute oral toxicity to rats), less toxic than difenoconazole (*e.g.*, 1,2,4-triazole and triazole acetic acid acute toxicity to freshwater fish and invertebrates), or more toxic than difenoconazole (*e.g.*, 1,2,4-triazole acute oral toxicity to birds) depending on the taxonomic group and exposure scenario. For example, 1,2,4-triazole will be a degradate of concern for acute toxicity to mammals and birds but will not be a degradate of concern for acute toxicity to freshwater fish and invertebrates.

Drinking Water Assessment

Difenoconazole and CGA-205375 will be considered the stressors of concern in the difenoconazole DWA, consistent with the conclusions of the Residues of Concern Knowledgebase Subcommittee (ROCKS) committee of the Health Effects Division (HED) (USEPA, 2011). The residues of concern may be reevaluated pending receipt and review of additional environmental fate and toxicity data. It is anticipated that the other two major degradates, 1,2,4-triazole and triazole acetic acid, will be addressed in an updated aggregate DWA.

Aggregate Risk Assessment

Aggregate risk from two of the major degradates, 1,2,4-triazole and its conjugate: triazole acetic acid, may be addressed in a separate ERA and DWA because they are common to the class of compounds known as triazoles (i.e., triazole-derivative fungicides, T-D fungicides, or conazoles).

6.2. Measures of Exposure

Difenoconazole concentrations in aquatic and terrestrial environments will be modeled using the maximum labeled application rates, the maximum number of applications, the minimum application intervals, and application methods that have the greatest potential for off-site transport.

Aquatic Exposure

There is potential for exposure to non-target organisms through run-off and spray drift. The most current models will be used to estimate residues in water at the time of the risk assessment (*e.g.*, SWCC). [16] Bioaccumulation potential in aquatic organisms will be estimated to assess exposure to piscivorus animals (*e.g.*, Kow (based) Aquatic BioAccumulation Model (KABAM)).[16]

A total toxic residue (TTR) approach will be used to estimate exposure to aquatic organisms. Degradate CGA-205375 will be included in the TTR of difenoconazole because it forms greater than 10% of applied difenoconazole in available fate studies and available information suggests that CGA-205375 and difenoconazole are equally toxic.

Terrestrial Exposure

There is potential for exposure to non-target organisms through consumption of contaminated food items (*e.g.*, treated insects or vegetation and contaminated fish), direct application, runoff, or spray drift. The most current models will be used at the time of the risk assessment. Current models include:

T-REX (v 1.5.2)[16] is used to estimate avian and mammal exposure residues on terrestrial food items. For input into T-REX, the default foliar dissipation half-life of 35 days will be used in the absence of acceptable foliar dissipation rate data.

TerrPlant (v 1.2.2)[16] is used to calculate EECs for characterizing exposure to terrestrial and semi-aquatic plants.

Terrestrial Investigation Model (TIM, v. 3.0 beta)[16] is used to derive quantitative estimates of the probability (or likelihood) and magnitude of mortality to birds.

6.3. Measures of Effect

Toxicity effects data will be used as measures of direct and indirect effects to biological receptors (USEPA, 2004). As discussed previously, data will be obtained from registrant-submitted studies and from literature studies identified in ECOTOX.

Quantitative assessment of risks will be based on study endpoints that can be directly linked to the Agency's assessment endpoints of impaired survival, growth, and reproduction. Sub-lethal

[16] http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/models-pesticide-risk-assessment

effects (*e.g.,* lethargy and changes in coloration) will be evaluated qualitatively. Available incident data will be used to further characterize risk.

6.4. Integration of Exposure and Effects

The exposure and effects data will be integrated in order to evaluate potential adverse ecological effects on non-target species. The risk quotient method will be used to compare exposure and measured toxicity values. EECs will be divided by acute and chronic toxicity values. The resulting RQs will be compared to the Agency's Levels of Concern (LOC) (USEPA, 2004).

6.5. Endangered Species Assessments

Consistent with EPA's responsibility under the Endangered Species Act (ESA), the Agency will evaluate risks to federally listed threatened and endangered (listed) species from registered uses of pesticides in accordance with the Joint Interim Approaches developed to implement the recommendations of the April 2013 National Academy of Sciences (NAS) report, *Assessing Risks to Endangered and Threatened Species from Pesticides*. The NAS report[17] outlines recommendations on specific scientific and technical issues related to the development of pesticide risk assessments that EPA and the Services (U.S. Fish and Wildlife Service and National Marine Fisheries) must conduct in connection with their obligations under the ESA and FIFRA. EPA will address concerns specific to difenoconazole in connection with the development of its final registration review decision for difenoconazole.

In November 2013, EPA, the Services, and USDA released a white paper containing a summary of their joint Interim Approaches for assessing risks to listed species from pesticides. These Interim Approaches were developed jointly by the agencies in response to the NAS recommendations, and reflect a common approach to risk assessment shared by the agencies as a way of addressing scientific differences between the EPA and the Services. Details of the joint Interim Approaches are contained in the November 1, 2013 white paper, *Interim Approaches for National-Level Pesticide Endangered Species Act Assessments Based on the Recommendations of the National Academy of Sciences April 2013 Report.* [18]

Given that the agencies are continuing to develop and work toward implementation of the Interim Approaches to assess the potential risks of pesticides to listed species and their designated critical habitat, this ecological problem formulation supporting the Preliminary Work Plan for difenoconazole does not describe the specific ESA analysis, including effects determinations for specific listed species or designated critical habitat, to be conducted during registration review. While the agencies continue to develop a common method for ESA analysis, the planned risk assessment for the registration review of difenoconazole will describe the level of ESA analysis completed for this particular registration review case. This assessment will allow EPA to focus its future evaluations on the types of species where the potential for effects exists, once the scientific methods being developed by the agencies have been fully vetted. Once the agencies have fully developed and implemented the scientific methods necessary to complete

[17] http://www.nap.edu/catalog/18344/assessing-risks-to-endangered-and-threatened-species-from-pesticides
[18] http://www2.epa.gov/endangered-species/interim-approaches-pesticide-endangered-species-act-assessments-based-nas-report

risk assessments for listed species and their designated critical habitats, these methods will be applied to subsequent analyses of difenoconazole as part of completing this registration review.

6.6. Endocrine Disruptor Screening

As required by Federal Food, Drug and Cosmetic Act (FFDCA) section 408(p), difenoconazole is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).[19] Difenoconazole is not in the first or second group of pesticide active ingredients to be screened under the EDSP.

6.7. Drinking Water Assessment

A DWA will be conducted, if warranted, to support future human health dietary risk assessments of difenoconazole. The residues of concern will be difenoconazole and CGA-205375 as recommended by the ROCKS committee (USEPA, 2011). The residues of concern may be reevaluated pending receipt and review of additional environmental fate and toxicity data. Concentrations in surface and groundwater will be estimated using current exposure models.[20] Additionally, EFED may update the previously conducted aggregate drinking water exposure assessment for 1,2,4-triazole and its conjugates.

6.8. Preliminary Identification of Data Gaps

Available studies submitted to fulfill environmental fate and ecological effects guideline requirements, as well as outstanding data gaps for difenoconazole are defined in **Sections 6.8.1** and **6.8.2**, respectively. Studies are identified that offer data for each guideline requirement, as well as study classifications and whether or not further data are needed in order to support the risk assessment.

6.8.1. Environmental Fate Data

Environmental fate data gaps for difenoconazole are indicated in the table below (**Table 11**).

EFED recommends requesting the following studies to reduce uncertainty in the risk assessment:

- 850.7100: ILV: Independent laboratory validation report for analytical method in soil for difenoconazole and its metabolites (CGA-205375, CGA-142856, and CGA-71019).
- 850.7100: ECM/ILV: Environmental chemistry methods and independent laboratory validation in water for difenoconazole and its metabolites (CGA-205375, CGA-142856, and CGA-71019).

<u>Major degradate (CGA-205375)</u>

There are no environmental fate studies available for CGA-205375 except for a soil batch equilibrium study (MRID 469501-23/24). In the absence of CGA-205375 environmental fate studies, needed physiochemical and environmental fate properties will be estimated using EPI

[19] http://www2.epa.gov/endocrine-disruption
[20] http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/models-pesticide-risk-assessment

Suite.[21] Study-sourced environmental fate and physicochemical properties of CGA-205375 may reduce the uncertainties in the aquatic exposure and drinking water assessments.

Table 11. Environmental Fate Data and Data Gaps for Difenoconazole

Guideline	Description	MRID	Classification	Data Gap?	Comments
835.2120	Hydrolysis	42245127	Acceptable	No	--
835.2240	Aqueous photolysis	42245128 46950104 46950105	Supplemental	No	--
835.2410	Soil photolysis	46950106	Supplemental	No	--
835.4100	Aerobic soil metabolism	42245131 42245132 42245133 46950109 46950110 46950111 469501-12 & -13 469501-14 & -15	Supplemental Supplemental Supplemental Supplemental Supplemental Supplemental Supplemental Supplemental	No	--
835.4200	Anaerobic soil metabolism	42245132 42245133	Supplemental Supplemental	No	Two anaerobic soil metabolism studies have already been submitted and are classified as supplemental. Additional data are required under 40 CFR Part 158 for terrestrial outdoor uses. Predicted DT_{50s} suggest that difenoconazole is stable under anaerobic conditions. Additional data are considered to have a low potential to add value to exposure assessments for the ecological risk and drinking water.
835.4300	Aerobic aquatic metabolism	42245134 46950116 46950117	Supplemental Supplemental Supplemental	No	--
835.4400	Anaerobic aquatic metabolism	42245134 46950119	Supplemental Supplemental	No	--
835.1230 835.1240	Adsorption/ desorption and leaching	42245135 42245136 46950121	Supplemental Supplemental Acceptable	No	--
835.1410	Volatility – laboratory	--	--	No	Difenoconazole is not expected to be volatile under normal use conditions based on low vapor pressure and Henry’s Law Constant

[21] Estimation Programs Interface (EPI) Suite™ is comprised of a set of programs that estimate fate and physical properties. It was developed by the EPA’s Office of Pollution Prevention Toxics and Syracuse Research Corporation (SRC).

Guideline	Description	MRID	Classification	Data Gap?	Comments
835.6100	Terrestrial field dissipation	42245140 46950126 46950127 46950129	Supplemental Acceptable Acceptable	No	---
850.6100	Analytical method in soil	46950128 (ECM)	Not applicable	**Yes**	Independent laboratory validations (ILV) is required for difenoconazole and its degradates.
	Analytical method in water	--	--	**Yes**	Environmental chemistry method (ECM) and independent laboratory validations (ILV) are required for difenoconazole and its degradates.
850.1730	Fish bioconcentration	42245142	Acceptable	No	---

BOLD = Recommended Studies

6.8.2. Ecological Effects Data

Data gaps for difenoconazole remain (**Tables 12, 13, and 14**); however, some of these studies are anticipated to have little impact on the risk assessment and are not recommended for a data-call in (DCI). EFED recommends requesting the following studies to reduce uncertainty in the risk assessment:[22]

- 850.4550: Cyanobacteria toxicity (difenoconazole; TGAI)*
- 850.4100: Terrestrial plant toxicity (seedling emergence) – (TEP)*
    - Tier II testing is required for lettuce, soybean, and sugar beet. A NOAEC must be established at the maximum single application rate (Tier 1 test) for the other seven test species (those showing no effects in the available study, MRID 48453203); alternatively, Tier II testing may be conducted for those species.
- 850.4150 : Terrestrial plant toxicity (vegetative vigor) – (TEP)*
    - A NOAEC must be established for all ten test species at the maximum single application rate (Tier I test). Alternatively, Tier II testing may be conducted.
- Non-guideline: Chronic toxicity to benthic invertebrates (whole sediment; 3 test species: freshwater amphipod, freshwater midge, and estuarine/marine amphipod) – (difenoconazole; TGAI)*
    - EFED recommends that the registrant consider Agency-wide guidelines for chronic testing of freshwater and estuarine/marine organisms[23,24] because the OCSPP 850 series guidelines are in the process of being finalized. A protocol must be submitted for review prior to initiating the studies.

[22] The studies marked with an asterisk (*) were recently required as a condition of registration for a PRIA label amendment for EPA Reg. No. 100-739 to add new uses to the label for use on Legumes Subgroup 6C and Bushberry Subgroup 13-07B; Related to Petition #4F8231 (May 6, 2015).
[23] USEPA 2000. Methods for Measuring the Toxicity and Bioaccumulation of Sediment-associated Contaminants with Freshwater Invertebrates. EPA 600/R-99/064
[24] USEPA 2001. Methods for Assessing the Chronic Toxicity of Marine and Estuarine Sediment-associated Contaminants with the Amphipod *Leptocheirus plumulosus*. EPA 600/R-01/020.

- Non-guideline Tier I: Honeybee adult acute oral exposure (difenoconazole; TGAI)
- Non-guideline Tier I: Honeybee adult chronic oral exposure (difenoconazole; TGAI)
- Non-guideline Tier I: Honeybee larval acute and chronic oral exposure (difenoconazole; TGAI)
- Non-guideline Tier II: Residue in pollen and nectar (recommendation pending risks identified in Tier I studies) (TEP)
- Non-guideline Tier II: semi-field testing for pollinators (tunnel and feeding studies) (recommendation pending risks identified in Tier I studies) (TEP)
- 850.3040: Tier III full-field testing for pollinators (recommendation pending risk identified in Tier II studies) (TEP)

Toxicity data from other sources (*e.g.*, other conazoles) may be used in the absence of data for difenoconazole. Use of surrogate data may over or underestimate risk of difenoconazole use.

Major degradates (CGA-205375, 1,2,4-triazole, and triazole acetic acid)

Data submission for CGA-205375, 1,2,4-triazole, and triazole acetic acid chronic toxicity would be welcomed and may reduce uncertainty in the risk assessment; however, EFED is not recommending degradate toxicity data at this time given that it is not anticipated that data would substantially change risk conclusions. Nonetheless, chronic toxicity data may be useful for refining risk concerns for birds, fish, and aquatic invertebrates. ECOSAR estimates suggest that CGA-205375 and difenoconazole are equally toxic to aquatic organisms (less than an order of magnitude difference in toxicity); therefore, equal toxicity will be assumed in the absence of data. ECOSAR estimates of 1,2,4-triazole and triazole acetic acid suggest that they are less toxic on a chronic basis than difenoconazole to aquatic organisms; thus, empirical data would be useful to confirm this assumption. Data indicate that 1,2,4-triazole is more acutely toxic to birds than difenoconazole, suggesting chronic toxicity of 1,2,4-triazole may be greater than difenoconazole as well. Although a chronic risk concern is expected for birds based on difenoconazole alone, 1,2,4-triazole data would be useful to confirm the assumption of greater toxicity and better characterize risk from difenoconazole use.

Table 12. Ecological Effects Data Requirements (TGAI) for Aquatic Organisms Exposed to Difenoconazole and Data Gaps[A]

Guideline	Description	MRID	Classification	Data Gap?	Comments
850.1075	Acute freshwater fish toxicity (cold water species)	42245107 42245108	Acceptable[1] Acceptable[1]	No	[1] In some cases an older classification scheme was reported in the DER. Studies classified as "core" are equivalent to "acceptable". [2] Upgraded to acceptable with submission of MRID 46950132.
	Acute freshwater fish toxicity (warm water species)	42245109 48453201	Acceptable[1] Acceptable	No	
	Acute estuarine/ marine fish toxicity	42245112 42906702	Acceptable[1] Acceptable[1]	No	

Guideline	Description	MRID	Classification	Data Gap?	Comments
850.1010	Acute toxicity to freshwater invertebrates	42245110	Acceptable[1]	No	[3] A definitive endpoint was established in MRID 49322901/49387801 but at a higher concentration than those showing effects in the two previously conducted studies (MRID 46950133 and 47648603). Given the available information, additional testing is unlikely to add substantial value to the risk assessment (conclusions) and is therefore not requested at this time. However, additional testing could be recommended in the future if it appears that it would impact the risk assessment (*see* detailed discussion in USEPA, 2014a). [4] There is some uncertainty in the results of the available early life stage study. A new study is not recommended because risk can be assessed using the acceptable life cycle study (MRID 48453205). [5] Although a study submission would be welcomed, EFED is not recommending a study at this time. Toxicity can be estimated using an acute-to-chronic ratio if data are not available. Available acute data suggest similar toxicity of difenoconazole to freshwater and marine/estuarine fish; thus, it is assumed that toxicity is similar on a chronic-basis too. It is assumed that the freshwater study is protective of marine-estuarine fish.
850.1025	Acute estuarine/ marine mollusk toxicity	42245113 42906701	Acceptable[1] Acceptable[1]	No	
850.1035	Acute estuarine/ marine invertebrate toxicity	42245111	Acceptable[1]	No	
850.1300	Freshwater invertebrate life cycle	42245114	Acceptable[2]	No	
850.1350	Saltwater invertebrate life cycle	46950133 47648603 49322901/49387801	Supplemental Supplemental Acceptable	No[3]	
850.1400	Freshwater fish early life stage	42245115	Supplemental	Yes[4]	
	Saltwater fish early life stage	-	-	Yes	
850.1500	Freshwater fish life cycle	48453205	Acceptable	No	
	Saltwater fish life cycle	-	-	Yes[5]	
850.1735	Whole sediment acute toxicity, freshwater invertebrates	47648601	Supplemental	No[6]	
850.1740	Whole sediment chronic toxicity, marine invertebrates	-	-	No	
-	Whole sediment chronic toxicity, freshwater invertebrates	-	-	**Yes**[7]	
-	Whole sediment chronic toxicity, marine-estuarine invertebrates	-	-	**Yes**[7]	
850.5400[B]	Aquatic plant growth (freshwater green alga)	46950212	Acceptable	No	
	Aquatic plant growth (freshwater diatom)	46950208	Acceptable	No	

Guideline	Description	MRID	Classification	Data Gap?	Comments
	Aquatic plant growth (saltwater diatom)	46950210	Acceptable	No	[6] The available study is a non-guideline range finding study that does not fill the data requirement for 850.1735. However, there is not a data gap because an acute study is not required. [7] Data are recommended because there is uncertainty associated with chronic risk to benthic invertebrates given that pore water EECs are similar to water column EECs and the chronic LOC (1.0) is exceeded for aquatic invertebrates based on comparison of water column species toxicity data to pore water EECs. Sediment chronic toxicity testing with three species is recommended: freshwater midge, freshwater amphipod, and marine/estuarine amphipod. [8] Testing with a TEP is typically recommended; however, TGAI testing is preferred to be consistent with available difenoconazole toxicity data for other aquatic plants. [9] A study is not recommended at this time as additional data are unlikely to have substantial impact on the risk assessment.
850.5400[B]	Aquatic plant growth (Cyanobacteria)	46950206	Invalid	**Yes**[8]	
850.4400[B]	Aquatic plant growth (vascular plants)	46950204	Supplemental	Yes[9]	

[A] An invalid early life stage (ELS) study was previously submitted for freshwater fish (MRID 45137502) but was subsequently replaced with a supplemental ELS study and an acceptable life cycle study.
[B]As of July 2012 the new guideline numbers are 850.4500 (Algal toxicity) and 850.4550 (Cyanobacteria toxicity)
BOLD = Recommended Studies

Table 13. Ecological Effects Data Requirements (TGAI) for Terrestrial Animals Exposed to Difenoconazole and Data Gaps[A]

Guideline	Description	MRID	Classification	Data Gap?	Comments
850.2100	Avian acute oral toxicity (upland game or waterfowl species)	42245105	Acceptable[1]	No[2]	[1] In some cases an older classification scheme was reported in the DER. Studies classified as "core" are equivalent to "acceptable". [2] Non-definitive endpoints were reported. Additional data are not needed nor recommended at this time. However, if the risk picture changes (*e.g.*, risk concerns cannot be precluded based on the available data due to greater exposure than is expected at this time based on current uses) then additional data could be recommended in the future. [3] Upgraded to acceptable with submission of MRID 46950201. [4] Data are needed to assess risk because an exposure pathway exists, some of the registered uses are pollinator attractive crops (USDA, 2015), and incidental residues may occur on other flowering plants (*e.g.* weeds) on or near the treatment site. [5] If Tier 1 screening risks are identified based on Tier I toxicity studies then Tier II studies (residue in pollen and nectar and 850.3040 semi-field testing for pollinators) could be recommended and if risks are identified based on Tier II assessment then Tier III studies could be recommended (850.3040 full-field testing for pollinators).
	Avian acute oral toxicity (passerine species)	48453202	Acceptable	No[2]	
850.2200	Avian dietary toxicity (upland game species)	42245103	Acceptable[1]	No	
	Avian dietary toxicity (waterfowl species)	42245104	Acceptable[1]	No[2]	
850.2300	Avian reproduction (upland game species)	46950202	Acceptable	No	
	Avian reproduction (waterfowl species)	42245106	Acceptable [3]	No	
850.3020	Adult honeybee acute contact toxicity (Tier 1)	42245124	Acceptable[1]	No[2]	
Non-guideline	Adult honeybee acute oral toxicity (Tier 1)	42245123	Invalid	**Yes**	
Non-guideline	Adult honeybee chronic oral toxicity (Tier 1)	-	-	**Yes**[4,5]	
Non-guideline	Larval honeybee acute and chronic oral toxicity (Tier 1)	-	-	**Yes**[4,5]	

[A] In some cases invalid studies were submitted [avian reproduction with an upland game species (MRID 42280601) and adult honeybee acute contact toxicity (MRID 42245123)] but were subsequently replaced with valid studies.
BOLD = Recommended Studies

Table 14. Ecological Effects Data Requirements (TEP) for Plants Exposed to Difenoconazole and Data Gaps

Guideline	Description	MRID	Classification	Data Gap?	Comments
850.4100[A]	Terrestrial plant toxicity (Tier I or Tier II seedling emergence)	48453203	Supplemental	**Yes**[1,2]	[1] The available Tier I study is supplemental because there were biologically significant effects observed in dicots at the limit test concentration which is below the maximum labeled single application rate (turf; 0.26 lb ai/A). Tier II testing is required for the dicot species that showed effects in the available study (lettuce, soybean, and sugar beet). Furthermore, a NOAEC must be established at the maximum single application rate (Tier 1 test) for the other seven test species (those showing no effects in the available study) to meet the data requirement; alternatively, Tier II testing may be conducted for those species. [2] It is EFEDs understanding that 0.26 lb ai/A is the maximum single application rate for all currently registered uses. The registrant should confirm the maximum registered rate prior to conducting any Tier I studies. [3] The available Tier I study is supplemental because the limit test concentration is below the maximum labeled single application rate (turf; 0.26 lb ai/A). To meet the data requirement, a NOAEC must be established for all ten test species at the maximum single application rate (Tier I test). Alternatively, Tier II testing may be conducted.
850.4150[B]	Terrestrial plant toxicity (Tier I or Tier II vegetative vigor)	48453204	Supplemental	**Yes**[2,3]	

[A] As of July 2012 the Final Guideline 850.4100 contains both Tier I and Tier II test guidance.
[B] As of July 2012 the Final Guideline 850.4150 contains both Tier I and Tier II test guidance.
BOLD = Recommended Studies

7. References

FAO. 2000. Appendix 2. Parameters of pesticides that influence processes in the soil. In FAO Information Division Editorial Group (Ed.), Pesticide Disposal Series 8. Assessing Soil Contamination. A Reference Manual. Rome: Food & Agriculture Organization of the United Nations (FAO). http://www.fao.org/docrep/003/x2570e/x2570e00.htm

USDA. 2015. Attractiveness of Agricultural Crops to Pollinating Bees for the Collection of Nectar and/or Pollen.

USEPA. 2004. Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs. U.S. Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances, Office of Pesticide Programs, Washington DC. January 23, 2004.

USEPA. 2011. Difenoconazole: Report of the Residues of Concern Knowledgebase Subcommittee (ROCKS). Health Effects Division, Office of Chemical Safety and Pollution Prevention. U. S. Environmental Protection Agency. DP 391350.

USEPA. 2013. Drinking Water Exposure Assessment in support of the new use registration of difenoconazole formulated product Inspire on Canola/Oilseed Subgroup 20A. Environmental Fate and Effects Division, Office of Chemical Safety and Pollution Prevention. U. S. Environmental Protection Agency. DP 412614.

USEPA. 2014a. Difenoconazole: Ecological Risk Assessment for Numerous Proposed New Uses and Changes to Registered Uses (Application Rate, Crop Groupings, and Additions to New Products). DP 417610^{+}.

USEPA. 2014b. Drinking Water Exposure Assessment in support of the new use registration of multiple difenoconazole formulated products on Artichoke, Berry Bushberry Subgroup 13-07B, Ginseng, and Bean and Pea, Dried Shelled (except Soybean) Subgroup 6C as well as Conversion of Stone Fruit Crop Group 12-12 and Tree Nuts Crop Group 14-12. Environmental Fate and Effects Division, Office of Chemical Safety and Pollution Prevention. U. S. Environmental Protection Agency. DP 421092.

USEPA. 2015. Myclobutanil Problem Formulation for Registration Review. DP 421959.

APPENDIX A. Difenoconazole Uses

Previous assessments are listed in **Table A-1**. The purpose of this table is to capture the historical range of assessed uses and rates and is not intended to constitute a comprehensive up-to-date list of currently registered uses and rates. Most uses allow aerial and ground applications and in some cases chemigation. In some cases a different mode of action fungicide should be alternated after a specified number of applications of difenoconazole containing products. The registration review risk assessment will be based on current label information at the time of assessment as provided by BEAD.

Table A-1. Previous Actions and Assessed Uses for Difenoconazole

Crop	Maximum Application Rate (lb ai/A)		Number of Applications (Minimum Application Interval (days))	Action DP Barcode (Date)
	Single	Seasonal/ Annual		
Ornamentals	0.13	0.52 /year (outdoor) or /crop (indoor)	4 (7)	ERA 417610, 418014, 418502, 421513, 421518, 421519, and 421523 (12/19/2014) DWA 421092 (11/13/2014)
Berry and small fruit; bushberry subgroup 13-07B Brassica (cole) leafy vegetables Bulb vegetables (green onion limited to 3 applications or 0.345 lb ai/A/year (outdoor crop) or per crop (indoor crop) Cucurbit vegetables Ginseng Legume vegetables; dried shelled pea and bean (except soybean) subgroup 6C Stone fruit (crop group 12-12)	0.115	0.46 /year (outdoor; all uses) or /crop (indoor; Brassica, bulb vegetables, and cucurbit vegetables)	4 (7)	
Artichoke Tree nuts (crop group 14-12)	0.115	0.46	4 (14)	
Cucurbit vegetables	0.114 + 0.064	0.52	4 +1 (7)	
Cucumber (greenhouse grown)	0.114	0.46	4 (7)	
Fruiting vegetables (except tomato)	0.113	0.45 /year (outdoor) or /crop (indoor)	4 (7)	
Tomato	0.0656	0.385 /year (outdoor) or /crop (indoor)	6 (7)	
Pome fruit (crop group 11-10)	Post-harvest treatment (dip, drench, flood, or spray)			

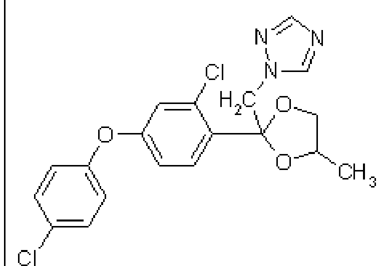
Crop	Maximum Application Rate (lb ai/A)		Number of Applications (Minimum Application Interval (days))	Action DP Barcode (Date)
	Single	Seasonal/ Annual		
Canola and oilseed subgroup 20A	0.113	NS (assumed 0.113)	NS (assumed 1 application/year)	ERA 409484 and 409488 (11/08/2013) DWA 412614 (8/14/2013)
Potato (seed treatment)	0.062	NA	NA	ERA 402993 and 404403 (8/29/2012)
Citrus	0.125	0.50	4 (7)	DWA - revised 395784 (12/20/2011)
Fruiting vegetable Low growing berry subgroup (except cranberry) Vegetable, tuberous and corm subgroup	0.114	0.46	4 (7)	
Pome fruit	0.07	0.35	5 (7)	
Carrot Chickpea Strawberry	0.114	0.46	4 (7)	ERA 378927 and 384074 (2/22/2011) DWA 378946 (9/27/2010) * Seed treatments were not included in the DWA.
Soybean	0.114	0.46	4 (7-14 depending on the formulation)	
Stone fruit (group 12)	0.114	0.46	4 (7-10 depending on the formulation)	
Oat (seed treatment)	0.023	NA	NA	
Rye (seed treatment)	0.034	NA	NA	
Golf course turf	0.26	0.52	2 (14)	ERA 377719 (7/28/2010) DWA 371044 (6/1/2010)
Citrus fruit	0.125	0.50	4 (7)	ERA 361251 (8/26/2009) DWA 361398 (5/28/2009) DWA - revised 398836 (2/23/2012)
Bulb vegetables (green onion)	0.114	0.34	3 (7)	
Brassica (cole) leafy vegetables Bulb vegetables (dry bulb) Cucurbit vegetables	0.114	0.46	4 (7)	
Grapes	0.114	0.46	4 (10)	
Almonds Filberts Pecans Pistachios Tree nuts	0.114	0.46	4 (14)	
Watermelon	0.114	0.228	2	Emergency Exemption for Indiana 353502 (7/3/2008)

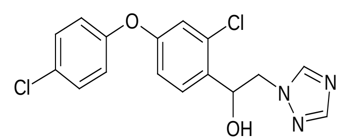
Crop	Maximum Application Rate (lb ai/A)		Number of Applications (Minimum Application Interval (days))	Action DP Barcode (Date)
	Single	Seasonal/ Annual		
Cucurbits- watermelons, cantaloupes, cucumbers	0.114	0.46	4	Emergency Exemption for Georgia 351238 (5/15/2008)
Almonds	0.11	N/A	2	Emergency Exemption for California 351716 (5/15/2008)
Ornamentals (carnations, gladiolus, irises, and roses)	0.13	0.56[1]	NS (7)	ERA 333319 and 340041 (7/12/2007) DWA 333319 and 340041 (5/1/2007 and 6/19/2007)
Fruiting vegetables Sugar beet Vegetables, tuberous and corm subgroup	0.11	0.44	NS (7)	
Pome fruit	0.07	0.35	NS (7)	
Barley (seed treatment) Corn, sweet (seed treatment) Cotton (seed treatment)	0.024 0.008 0.006	NA NA NA	NA NA NA	ERA 316708, 316620, and 316707 (9/21/2005)
Wheat (seed treatment)	0.044	NA	NA	DWA 307166 (5/2/2005)
Canola (seed treatment)	0.00192	NA	NA	ERA and DWA 252640 (5/30/2001)
Canola (seed treatment)	0.0013	NA	NA	Emergency Exemption for North Dakota 260762 (12/20/1999)
Wheat (seed treatment)	0.031	NA	NA	DWA 252509 (2/9/1999)
Wheat (seed treatment)	0.015	NA	NA	DWA Unknown DP (10/27/1998)
Wheat (seed treatment) Barley (seed treatment)	0.010	NA	NA	ERA 194836, 194830, 194872 and 194874 (3/29/1994)
Wheat (seed treatment)	1 oz per 100 lb seed	NA	NA	Emergency Exemption for Idaho 194787 (9/29/1993)

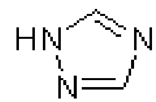
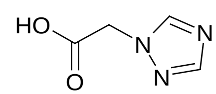
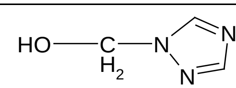
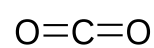
NA = Not applicable
NS = Not specified
[1] The 2007 ERA and DWA seem to have erroneously reported the annual rate as 0.56 lb ai/A. The correct rate is 0.52 lb ai/A

APPENDIX B. Names and Structures of Difenoconazole and its Major and Minor Degradates

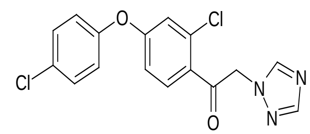
Table B-1

Code Name (Synonym)	Chemical Name	Chemical Structure	Study Type	MRID	Maximum %AR (day)	Final %AR (study length)
			PARENT			
Difenoconazole (CGA-169374)	**IUPAC Name:** 3-Chloro-4-[(2RS,4RS;2RS,4SR)-4-methyl-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]phenyl 4-chlorophenyl ether. **CAS Name:** 1-[2-[2-Chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-ylmethyl]-1H-1,2,4-triazole. **CAS Number:** 119446-68-3 **Formula:** $C_{19}H_{17}Cl_{2}N_{3}O_{3}$ **MW:** 406.3 **SMILES:** O1CC(C)OC1(Cn2ncnc2)c3c(Cl)cc(Oc4ccc(Cl)cc4)cc3		Hydrolysis pH 5	42245127	Not applicable	stable
			Hydrolysis pH 7			stable
			Hydrolysis pH 9			stable
			Aqueous Photolysis	42245128		2.50 (30 days)
				46950104		1.21 ± 0.5 (30 days)
				46950105		94.1 (15 days)
			Soil Photolysis	46950106 46950107		91.4 (30 days)
			Aerobic Soil Metabolism	46950109		18.4 ± 0.1 (293 days)
				46950110		14.1 (293 days)
				46950111		38.7 (228 days)
				46950112 46950113		57.6 (360 days)
				46950114 46950115		59.6 (372 days)
			Aerobic Aquatic Metabolism	46950116		71.2 (183 days)
				46950117 46950118		81.53 ± 3.22 (112 days)
			Anaerobic Aquatic Metabolism	46950119 46950120		42.72 ± 0.88 (350 days)

Code Name (Synonym)	Chemical Name	Chemical Structure	Study Type	MRID	Maximum %AR (day)	Final %AR (study length)
Difenoconazole (CGA-169374)			Terrestrial Field Dissipation	46950126	Not applicable	44 ppb (531 days)
				46950127		14 ppb (535 days)
				46950129		302 ppb (422 days)
MAJOR (>10%) TRANSFORMATION PRODUCTS						
CGA-205375 (CGA-179500, CGA-211391, and M1)	**CAS Name:** alpha-[2-Chloro-4-(4-chlorophenoxy)phenyl]-1H-1,2,4-triazole-1-ethanol. 1-[2-Chloro-4-(4-chlorophenoxy)phenyl]-2-[1,2,4]-triazol-1-yl-ethanol. **CAS Number:** 117018-19-6		Aqueous Photolysis	42245128	2.9 (5 days)	0.1 (30 days)
				46950104	2.04 (14 days)	0.96 (30 days)
				46950105	NA	NA
			Aerobic Soil metabolism	46950109	5.1 ± 1.4 (84 days)	3.7 ± 0.1 (293 days)
				46950110	4.6 ± 0.1 (56 days)	3.7 ± 0.5 (293 days)
				46950111	4.4 ± 1.6 (120 days)	2.7 (293 days)
				46950112 46950113	14.8 ± 1.8 (360 days)	14.8 ± 1.8 (360 days)
				46950114 46950115	9.4 ± 0.1 (372 days)	9.4 ± 0.1 (372 days)
			Aerobic Aquatic Metabolism	46950116	6.2 (183 days)	6.2 (183 days)
			Anaerobic Aquatic Metabolism	46950119 46950120	12.60 ± 0.42 (175 days)	6.2 ± 0.76 (350 days)
			Terrestrial Field Dissipation	46950126	11 ppb (358 days)	6.2ppb (531 days)
				46950127	12 ppb (123 days)	5.6 ppb (531 days)
				46950129	18ppb (364 days)	12.0 2ppb (535 days)

Code Name (Synonym)	Chemical Name	Chemical Structure	Study Type	MRID	Maximum %AR (day)	Final %AR (study length)
1,2,4-triazole (CGA-71019)	**CAS Name:** 1H-1,2,4-Triazole **CAS Number:** 288-88-0		Aqueous Photolysis	42245128	13.4 (9 days)	10.9 (30 days)
				46950104	12.27 ± 0.7 (30 days)	12.27 ± 0.7 (30 days)
				46950105	NA	NA
			Aerobic Soil Metabolism	46950110	20.6 (190 days)	17.8 ± 2.8 (293 days)
				46950111	1.6 ± 0.4 (120 days)	0.9 (228 days)
				46950114 46950115	7.8 ± 0.1 (372 days)	7.8 ± 0.1 (372 days)
			Anaerobic Aquatic Metabolism	46950119 46950120	35.92 ± 0.71 (350 days)	35.92 ± 0.71 (350 days)
			Terrestrial Field Dissipation	46950129	3.5 ppb (36 days)	< LOQ (535 days)
1,2,4-triazole acetic acid (CGA-142856)	**CAS Name:** 1H-1,2,4-Triazole-1-acetic acid **CAS Number:** 28711-29-7		Aqueous Photolysis	46950104	41.83 ± 0.9 (30 days)	41.83 ± 0.9 (30 days)
			Terrestrial Field Dissipation	46950126	<LOQ	11 ppb (358 days)
CGA-107069	**CAS Name:** 1H-1,2,4-Triazole-1-methanol **CAS Number:** 74205-82-6		Aqueous Photolysis	46950104	Reported as combined residue with 1,2,4-triazole	
Carbon dioxide	**CAS Number**: 124-38-9 **Formula:** CO_2 **MW:** 44.1 g/mol		Aqueous Photolysis	46950104	2.01 (30 days)	2.01 ± 2.5 (30 days)
				46950105	0.01 (3 days)	<0.1 (15 days)
			Soil Photolysis	46950106 46950107	0.02 (21 days)	<0.2 (30 days)
			Aerobic Soil Metabolism	46950109	23.4 ± 1.9 (293 days)	23.4 ± 1.9 (293 days)
				46950110	4.5 ± 2.4 (293 days)	4.5 ± 2.4 (293 days)

Code Name (Synonym)	Chemical Name	Chemical Structure	Study Type	MRID	Maximum %AR (day)	Final %AR (study length)
Carbon dioxide			Aerobic Soil Metabolism	46950111	19.2 (228 days)	19.2 (228 days)
				46950112 46950113	15.0 ± 1.3 (360 days)	15.0 ± 1.3 (360 days)
				46950114 46950115	4.2 ± 0.1 (372 days)	4.2 ± 0.1 (372 days)
			Aerobic Aquatic Metabolism	46950116	3.0 (183 days)	3.0 (183 days)
				46950117 46950118	0.59 ± 0.28 (98 days)	0.29 ± 0.03 (112 days)
			Anaerobic Aquatic Metabolism	46950119 46950120	0.55 ± 0.33 (245 days)	0.25 ± 0.02 (350 days)
Non-extractable Residues	Not identified	Not identified	Aerobic Soil Metabolism	46950109	38.0 ± 1.3 (293 days)	38.0 ± 1.3 (293 days)
				46950110	48.9 ± 0.6 (293 days)	48.9 ± 0.6 (293 days)
				46950111	22.9 (228 days)	22.9 (228 days)
				46950112 46950113	14.4 ± 1.0 (360 days)	14.4 ± 1.0 (360 days)
				46950114 46950115	18.4 ± 1.0 (360 days)	14.4 ± 1.0 (372 days)
			Aerobic Aquatic Metabolism	46950116	13.9 (183 days)	13.9 (183 days)
				46950117 46950118	8.87 ± 3.04 (112 days)	8.87 ± 3.04 (112 days)
			Anaerobic Aquatic Metabolism	46950119 46950120	8.06 ± 1.24 (302 days)	7.11 ± 0.32 (350 days)
Unidentified[1] Unknowns	Not identified	Not identified	Aqueous Photolysis	42245128	20.0 (15 days)	6.5 (30 days)
				46950104	29.02 ± 2.9 (30 days)	29.02 ± 2.9 (30 days)
				46950105	16.7 (15 days)	11.1 (15 days)

Code Name (Synonym)	Chemical Name	Chemical Structure	Study Type	MRID	Maximum %AR (day)	Final %AR (study length)
Unidentified[1] Unknowns			Aerobic Soil Metabolism	46950111	0.4 (228 days)	0.4 (228 days)
MINOR (<10%) TRANSFORMATION PRODUCTS						
CGA-205374 (CGA-176459)	**CAS Name:** 1-[2-Chloro-4-(4-chlorophenoxy)phenyl]-2-(1H-1,2,4-triazol-1-yl)-ethanone. **CAS Number:** 136815-80-0		Aqueous Photolysis	42245128	1.5 (0 day)	< LOQ (30 days)
				46950104	1.11 ± 0.11 (14 days)	0.13 ± 0.1 (30 days)
				46950105	NA	NA
			Aerobic Soil Metabolism	46950114 46950115	2.1 ± 0.4 (272 days)	1.4 ± 0.1 (293 days)
			Anaerobic Aquatic Metabolism	46950119 46950120	0.77± 0.23 (245 day)	LOQ (350 days)
M2	Not identified	Not identified	Aerobic Soil Metabolism	46950109	1.5 (28 days)	1.4 ± 0.1 (293 days)
				46950110	2.1 ± 1.81 (293 days)	2.1 ± 1.81 (293 days)
				46950111	1.5 (228 days)	1.5 (228 days)
			Anaerobic Aquatic Metabolism	46950119 46950120	5.79 ± 1.42 (245 days)	< LOQ (350 days)
M4	Not identified	Not identified	Aerobic Soil Metabolism	46950109	1.2 (190 days)	1.0 ± 0.4 (293 days)

NA = Not Analyzed

LOQ = Limit of Quantitation (1ppb)

[1] Unidentified unknowns consist of M4, M5, M6, and several unidentified components ranging from 0.5% to 9.7% of the applied radioactivity at study termination.

APPENDIX C. ECOSAR Results

Table C-1. Comparative Aquatic Toxicity of Difenoconazole and Major Degradation Products

Compound	FW fish 96-hr acute LC_{50} (mg/L)	FW fish chronic NOAEC (mg/L)[1]	FW invertebrate 48-hr acute EC_{50} (mg/L)	FW invertebrate chronic NOAEC (mg/L)[1]	ME fish 96-hr acute LC_{50} (mg/L)	ME fish chronic NOAEC (mg/L)[1]	ME invertebrate 96-hr acute LC_{50} (mg/L)	ME invertebrate chronic NOAEC (mg/L)[1]	Non-vascular plant 96-hr EC_{50} (mg/L)
Difenoconazole	**0.87** (*0.81*)	**0.007** (*0.0009*)	**0.95** (*0.77*)	**0.030** (*0.006*)	(*0.82*)	(*0.0009*)	(*0.15*)	(*<0.000115*)	**0.51** (*0.30*)[2]
1,2,4-triazole	**722.0** (*498.0*)	**2.2**	**3166.2** (*>98.0*)	**29.2**	-	-	-	-	**35.7** (*14.0*)[2]
Triazole acetic acid	**51322.1** (*>101.0*)	**132.3**	**281000.0** (*>108.0*)	**2132.3**	-	-	-	-	**1716.9**
CGA-205375	**2.79**	**0.022**	**2.6**	**0.179**	**8.36**[3]	**0.099**	**0.870**	**0.252**	**1.33**

[1] ECOSAR estimated chronic value is defined as the geometric mean of the no observed effect concentration (NOEC) and the lowest observed effect concentration (LOEC).

[2] Green algae

[3] Endpoint exceeds predicted water solubility of compound.

BOLD values are ECOSAR (v1.00) toxicity estimates (lowest toxicity value if multiple ECOSAR classes are available, *i.e.*, the most toxic).

Italic values are from submitted toxicity studies (most sensitive endpoint if multiple are available)

FW = freshwater and ME = marine/estuarine

APPENDIX D. SIP v.1.0 Inputs and Outputs

Table D-1. Inputs

Parameter	Value
Chemical name	Difenoconazole
Solubility (in water at 25ºC; mg/L)	15
Mammalian LD_{50} (mg/kg-bw)	1453
Mammalian test species	laboratory rat
Body weight (g) of "other" mammalian species	
Mammalian NOAEL (mg/kg-bw)	1.25
Mammalian test species	laboratory rat
Body weight (g) of "other" mammalian species	
Avian LD_{50} (mg/kg-bw)	2150
Avian test species	Mallard duck
Body weight (g) of "other" avian species	
Mineau scaling factor	1.15
Mallard NOAEC (mg/kg-diet)	110.8
Bobwhite quail NOAEC (mg/kg-diet)	21.9
NOAEC (mg/kg-diet) for other bird species	0
Body weight (g) of other avian species	0
NOAEC (mg/kg-diet) for 2nd other bird species	0
Body weight (g) of 2nd other avian species	0

Table D-2. Mammalian Results

Parameter	Acute	Chronic
Upper bound exposure (mg/kg-bw)	2.5800	2.5800
Adjusted toxicity value (mg/kg-bw)	1117.5903	0.9615
Ratio of exposure to toxicity	0.0023	2.6834
Conclusion*	**Drinking water exposure alone is NOT a potential concern for mammals**	**Exposure through drinking water alone is a potential concern for mammals**

Table D-3. Avian Results

Parameter	Acute	Chronic
Upper bound exposure (mg/kg-bw)	12.1500	12.1500
Adjusted toxicity value (mg/kg-bw)	1116.3346	2.3279
Ratio of exposure to acute toxicity	0.0109	5.2192
Conclusion*	**Drinking water exposure alone is NOT a potential concern for birds**	**Exposure through drinking water alone is a potential concern for birds**

*Conclusion is for drinking water exposure alone. This does not combine all routes of exposure. Therefore, when aggregated with other routes (*i.e.*, diet, inhalation, dermal), pesticide exposure through drinking water may contribute to a total exposure that has potential for effects to non-target animals.

APPENDIX E. STIR v.1.0 Inputs and Outputs

Table E-1. Input

Application and Chemical Information	
Enter Chemical Name	Difenoconazole
Enter Chemical Use	turf
Is the Application a Spray? (enter y or n)	y
If Spray What Type (enter ground or air)	ground
Enter Chemical Molecular Weight (g/mole)	406.27
Enter Chemical Vapor Pressure (mmHg)	2.50E-10
Enter Application Rate (lb ai/acre)	0.26
Toxicity Properties	
Bird	
Enter Lowest Bird Oral LD_{50} (mg/kg-bw)	2150
Enter Mineau Scaling Factor	1.15
Enter Tested Bird Weight (kg)	1.58
Mammal	
Enter Lowest Rat Oral LD_{50} (mg/kg-bw)	1453
Enter Lowest Rat Inhalation LC_{50} (mg/L)	>3.3[1]
Duration of Rat Inhalation Study (hr)	4
Enter Rat Weight (kg)	0.35

[1] MRID 42090008

Table E-2. Output

Results Avian (0.020 kg)		
Maximum Vapor Concentration in Air at Saturation (mg/m^3)	5.47E-06	
Maximum 1-hour Vapor Inhalation Dose (mg/kg)	6.87E-07	
Adjusted Inhalation LD_{50}	1.96E+01	
Ratio of Vapor Dose to Adjusted Inhalation LD_{50}	3.50E-08	*Exposure not Likely Significant*
Maximum Post-treatment Spray Inhalation Dose (mg/kg)	2.75E-02	
Ratio of Droplet Inhalation Dose to Adjusted Inhalation LD_{50}	1.40E-03	*Exposure not Likely Significant*

Results Mammalian (0.015 kg)		
Maximum Vapor Concentration in Air at Saturation (mg/m^3)	5.47E-06	
Maximum 1-hour Vapor Inhalation Dose (mg/kg)	8.64E-07	
Adjusted Inhalation LD_{50}	1.96E+02	
Ratio of Vapor Dose to Adjusted Inhalation LD_{50}	4.40E-09	*Exposure not Likely Significant*
Maximum Post-treatment Spray Inhalation Dose (mg/kg)	3.45E-02	
Ratio of Droplet Inhalation Dose to Adjusted Inhalation LD_{50}	1.76E-04	*Exposure not Likely Significant*